

# Pegvisomant for the Treatment of *gsp*-Mediated Growth Hormone Excess in Patients with McCune-Albright Syndrome

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**Context:** GH excess affects approximately 20% of the patients with McCune-Albright syndrome (MAS). MAS is caused by sporadic, postzygotic, activating mutations in the *GNAS* gene, which codes for the cAMP-regulating protein,  $G_s\alpha$  (*gsp* oncogene). These same mutations are found in approximately one third of the sporadic cases of acromegaly.

**Objective:** We examined efficacy of the GH receptor antagonist, pegvisomant, in controlling *gsp* oncogene-mediated GH excess and skeletal disease (fibrous dysplasia of bone) associated with MAS.

**Setting and Patients:** Five MAS patients with GH excess were treated with 20 mg/d sc injection of pegvisomant for 12 wk in a randomized, double-blind, placebo-controlled crossover study at the National Institutes of Health.

**Main Outcome Measures:** The primary measure of efficacy was normalization of IGF-I. Secondary outcome measures were reduction

in serum IGF binding protein-3 (IGFBP-3), improvement of fatigue and sweating, and reduction in markers of bone metabolism and bone pain.

**Results:** Combined mean changes in serum IGF-I at 6 and 12 wk were  $-236.4$  ng/ml (53%,  $P < 0.005$ ) and  $-329.8$  ng/ml (62%,  $P < 0.001$ ), respectively. IGFBP-3 decreased by 0.8 mg/liter (24%,  $P < 0.01$ ) and 2.9 mg/liter (37%,  $P < 0.005$ ), respectively. There were no significant changes in signs and symptoms of acromegaly or markers of bone metabolism and bone pain, nor was there a significant change in pituitary size. Retrospective comparison of the degree of control achieved with pegvisomant *vs.* other medications (long-acting octreotide  $\pm$  dopamine agonist) in the same group showed that the two regimens were similarly effective.

**Conclusions:** Pegvisomant effectively reduced IGF-I and IGFBP-3 levels in *gsp*-mediated GH excess but had no effect on fibrous dysplasia. (*J Clin Endocrinol Metab* 91: 2960–2966, 2006)

MCCUNE-ALBRIGHT SYNDROME (MAS) is classically defined clinically by the triad of polyostotic fibrous dysplasia of bone (FD), café-au-lait skin pigmentation, and hyperfunctioning endocrinopathies, such as precocious puberty (PP), GH excess (acromegaly), hyperthyroidism, hypercortisolism, and renal phosphate wasting associated with rickets/osteomalacia (1–3). The underlying molecular etiology of MAS is a postzygotic mutation of the *GNAS* gene (R201H,C,S,G) that encodes for the  $\alpha$ -subunit of the stimulatory heterotrimeric G protein complex,  $G_s\alpha$  (4, 5). These result in a constitutive activation of the adenylyl cyclase enzyme signal transduction pathway and dysregulated production of cAMP (6). The constellation of phenotypic presentations seen in MAS is an example of mosaicism and results from the involvement of cells in the affected tissues that harbor the *gsp* mutation and respond to the hormone-sensitive adenylyl cyclase signal transduction pathway.

About 20% of MAS patients have GH excess (7, 8). How-

ever, the diagnosis of GH excess in MAS is sometimes difficult. In children with MAS, rapid linear growth as a sign of GH excess is often ascribed to PP, which is seen in the majority of patients with MAS. And whereas patients with PP would be expected to have diminished final height, those with concomitant GH excess often attain (or exceed) the predicted midparental height. Therefore, normal stature in a person with MAS and PP can be a sign of GH excess (8). Additionally, the diagnosis is often delayed or missed because the characteristic coarsening of the face, frontal bossing, and prognathism evolve insidiously and may be obscured or attributed to the progression of the fibrous dysplastic bone lesions in the skull, which themselves can lead to some degree of dysmorphism in the absence of GH excess. It is important to diagnose and treat GH excess in MAS because GH excess is a risk factor for loss of vision and hearing (due to GH-fueled expansion of FD) as well as dramatic macrocephaly and dysmorphism (8, 9).

The same mutations in  $G_s\alpha$  that are found in MAS are present in the adenomatous tissue of approximately one third of the patients with sporadic acromegaly, suggesting that these mutations may also be the molecular etiology in those sporadic cases of sporadic acromegaly. GH plays a central role in skeletal development and maintenance, both through direct effects and those mediated by IGF-I (10). IGFs circulate by binding to six different types of IGF binding

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Abbreviations: FD, Fibrous dysplasia of bone; IGFBP, IGF binding protein; LAR, long-acting sandostatin; MAS, McCune-Albright syndrome; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; PP, precocious puberty.

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**TABLE 1.** Demographics and clinical and molecular characterization of the study cohort

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (yr)	33	39	17	37	13
Gender	Male	Female	Male	Female	Female
Weight (kg)	127	62	78	76	52
Pituitary adenoma on MRI	Yes	No	No	Yes	Yes
Baseline random GH (NR = 0–5.0 ng/ml)	75.6	7.4	5.6	23.4	17.3
Baseline IGF-I (ng/ml; Z score)	734 (8.2)	270 (0.6)	460 (1.8)	554 (4.6)	436 (1.8)
Serum GH at 60 and 120 min after OGTT (ng/ml)	101, 60.2	6.1, 3.9	2.2, 1.2	16, 14.3	16.3, 14.8
Fibrous dysplasia	Polyostotic	Polyostotic	Polyostotic	Polyostotic	Polyostotic
<i>GNAS</i> mutation <sup>a</sup>	Arg201Cys	Arg201Cys	Arg201Cys	Arg201Cys	Arg201His
Skeletal disease burden score <sup>b</sup>	58.3	17.7	58.2	23.7	59.5
Baseline head circumference (cm)	85	60	66	69	59
Previous GH excess therapy <sup>c</sup>	LAR(30) + DA(2)	LAR(30) + DA(2)	LAR(30) + DA(2)	LAR(30) + DA(8)	LAR(30) + DA(1)
Effective drug therapy	None	LAR	LAR	LAR	LAR+DA
Other endocrinopathies	PP, LT, RPW	n/a	PP, HT, LT, ST	PP	PP, HT, RPW

n/a, Not applicable; HT, hyperthyroidism; LT, Leydig cell tumor of testes; RPW, renal phosphate wasting; ST, Sertoli cell tumor of the testes; NR, normal range.

<sup>a</sup> Substitution of the amino acid cysteine (Cys) or histidine (His) for arginine at position 201 determined from bone specimen.

<sup>b</sup> See Ref. 14.

<sup>c</sup> (30), 30 mg/month; DA, dopamine agonist; (), dose of cabergoline per week.

proteins (IGFBPs), of which IGFBP-3 is the most abundant (11, 12) and in some cases may be a sensitive marker for GH excess.

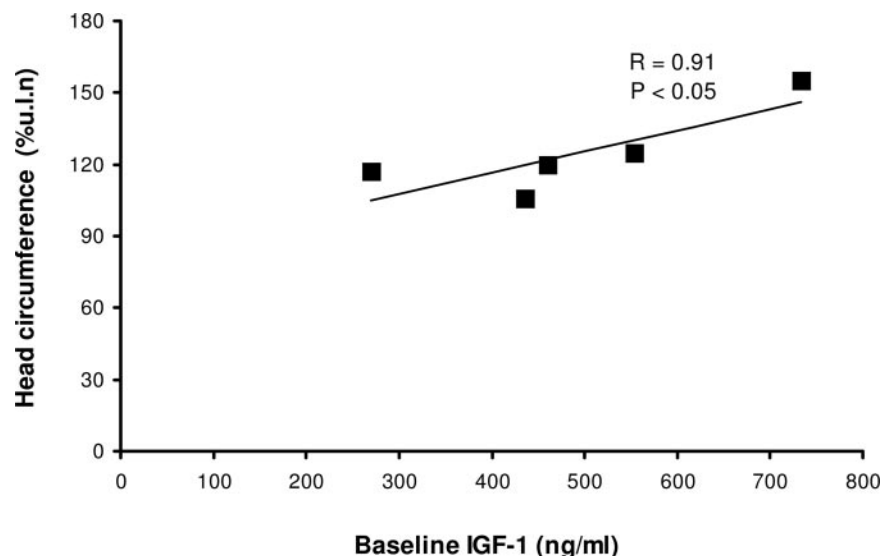
Conventional treatments of GH excess include surgery, medications, and radiotherapy. However, in patients with MAS, transphenoidal surgery is often not possible due to massive thickening of the skull base with FD, and radiation therapy is avoided because FD is prone to sarcomatous transformation after radiation (13). Therefore, medical therapy is often the only reasonable choice. Medical options include short- and long-acting analogs of somatostatin, dopamine receptor agonists, and more recently the GH receptor antagonist, pegvisomant. Somatostatin analogs and/or dopamine receptor agonists are not always effective in MAS (8), and it is unclear whether controlling GH excess affects FD. In addition, there has not been a report on the efficacy of a medical treatment of GH excess in a population of patients whose disease is of a single molecular etiology. Therefore, we tested the efficacy of pegvisomant in a population of patients with

MAS in normalizing serum IGF-I and, secondarily, its ability to decrease serum IGFBP-3, signs and symptoms of GH excess, bone pain and markers of bone metabolism in the FD associated with MAS.

## Patients and Methods

### Design

The study was a double-blinded, placebo-controlled, crossover study. Before enrollment, there was a 12-wk washout period during which all medications for the treatment of GH excess were discontinued. Subjects were randomized to either drug or placebo for 12 wk, after which there was a 6-wk washout period. Subjects were then crossed over to placebo or drug for the final 12 wk. The primary measure of pegvisomant efficacy was the age- and gender-specific normalization of serum IGF-I. Secondary measures of efficacy were normalization of serum level of IGFBP-3, improvement in signs and symptoms of GH excess (sweating and fatigue), decrease in serum and urine markers of bone metabolism, and a decrease in bone pain. Serum and urine samples were collected at baseline and wk 6, 12, 18, 24, 30, and 36. Liver function tests, hemogram, and electrocardiogram were performed to monitor for adverse effects. Change in pituitary size was assessed as a measure of drug safety



**FIG. 1.** Correlation between baseline serum IGF-I and head circumference. There was a significant association between head circumference (expressed as percent of the age- and gender-specific upper limit of normal) and baseline serum IGF-I. This is a reflection of macrocephaly, a GH excess-related morbidity in MAS.

TABLE 2. IGF-I and IGFBP-3 response to treatment

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Change from baseline	
	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Mean change (%)	P value <sup>a</sup>
IGF-I (ng/ml; Z-score)												
Baseline	734 (8.2)	796 (9.2)	269 (0.6)	270 (0.6)	483 (1.4)	460 (1.1)	554 (4.6)	797 (8.1)	436 (0.2)	421 (0.5)		
Week 6	687 (7.4)	626 (6.4)	293 (1.0)	107 (−1.6)	424 (0.6)	215 (−2.2)	838 (8.6)	374 (2.1)	488 (0.6)	105 (−2.7)	−263 (−53)	<0.005
Week 12	768 (8.7)	413 (3.0)	301 (1.1)	90 (−1.9)	494 (1.6)	191 (−2.5)	872 (9.1)	303 (1.1)	450 (0.3)	98 (−2.8)	−329 (−63)	<0.001
% change	−48		−67		−58		−65		−75			
Normal range	132–333		106–368		281–510		106–368		176–442			
IGFBP-3 (mg/liter) <sup>b</sup>												
Baseline	4.4	4.9	3.4	2.8	4.1	4.0	4.3	5.3	3.9	3.6		
Week 6	3.9	3.8	3.5	1.9	3.8	3.2	5.8	5.0	4.3	2.1	−0.8	<0.01
Week 12	5.1	2.5	3.3	1.9	4.3	2.7	5.6	3.8	4.0	2.1	−24%	<0.005
% change	−49		−32		−32		−28		−42		−37%	

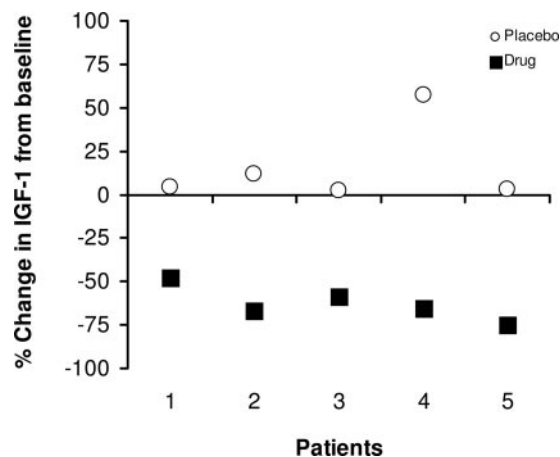
<sup>a</sup> Relative to placebo.<sup>b</sup> Normal range = 1.9–3.6; in patients 3 and 5, normal range of IGF-I and IGFBP-3 was adjusted for bone age.

FIG. 2. Percent change of serum IGF-I during the course of the study. The change in the serum IGF-I in comparison with the baseline (study entry) value during the pegvisomant treatment (filled squares) and placebo (open circles) phases are shown. During the pegvisomant phase, the serum IGF-I decreased an average of 63% from baseline. Patient 4 experienced a 57% increase in serum IGF-I during the course of the placebo phase of the study.

with magnetic resonance imaging (MRI) scanning at baseline and 1 yr. Pegvisomant was kindly provided by Pfizer Inc. (New York, NY; Pharmacia at the initiation of the study) as single-use, 20-mg strength lyophilized powder that was reconstituted with 1 ml saline for injection. Each vial of pegvisomant or placebo also contained 1.36 mg glycine, 36 mg mannitol, 1.04 mg sodium phosphate, dibasic (anhydrous), and 0.36 mg monobasic sodium phosphate. Both pegvisomant and placebo appeared similar in color after reconstitution. When a patient was on pegvisomant, the first dose was a loading dose of 40 mg followed by daily sc administration of 20 mg. The study was approved by the Institutional Review Board of the National Institute of Dental and Craniofacial Research, National Institutes of Health.

### Patients

Five patients were studied. There were 10 patients (adults and children) in the NIH cohort who were eligible for enrollment. Five declined enrollment for personal reasons, which included unwillingness to discontinue medical treatment for the washout period. MAS was diagnosed by a combination of clinical history; characteristic radiographic and histological features of FD; endocrine testing; and, when necessary, analysis of *GNAS* gene mutation. The age range was 13–39 yr, with a mean of 28 yr (Table 1). GH excess was diagnosed by clinical signs and symptoms of GH excess, elevated serum GH and IGF-I levels, but the key criterion for the diagnosis was a serum GH that did not suppress less than 1 ng/ml at 60 min on a standard oral glucose tolerance test (OGTT). Patient 2 (Table 1) had a normal IGF-I at baseline but a GH that did not suppress on OGTT and complications known to be associated with GH excess; one optic nerve decompression, and six facial/sinus operations. None of the patients had had pituitary surgery, due to the fact that either a pituitary adenoma was not visualized or they were considered inoperable due to the thickness of the skull base. None of the patients had prior radiotherapy because radiotherapy is a risk factor for transformation of FD to a malignancy (13) and is used only as a last resort. All patients had significant skeletal disease burden of FD (14). Four of the five patients had a history of other endocrine disorders, but only three had a demonstrable pituitary adenoma by MRI (Table 1).

### Methods

Serum IGF-I and IGFBP-3 were measured by RIA (Esoterix Inc., Austin TX). Serum IGF-I Z-scores were computed using reference ranges specific for the IGF-I assay. Serum GH was measured using a commercial immunochemiluminometric assay (Mayo Medical Laboratories, Rochester, MN) that was modified to avoid cross-reactivity with pegvisomant. Antipegvisomant antibodies were measured by MDS Pharma

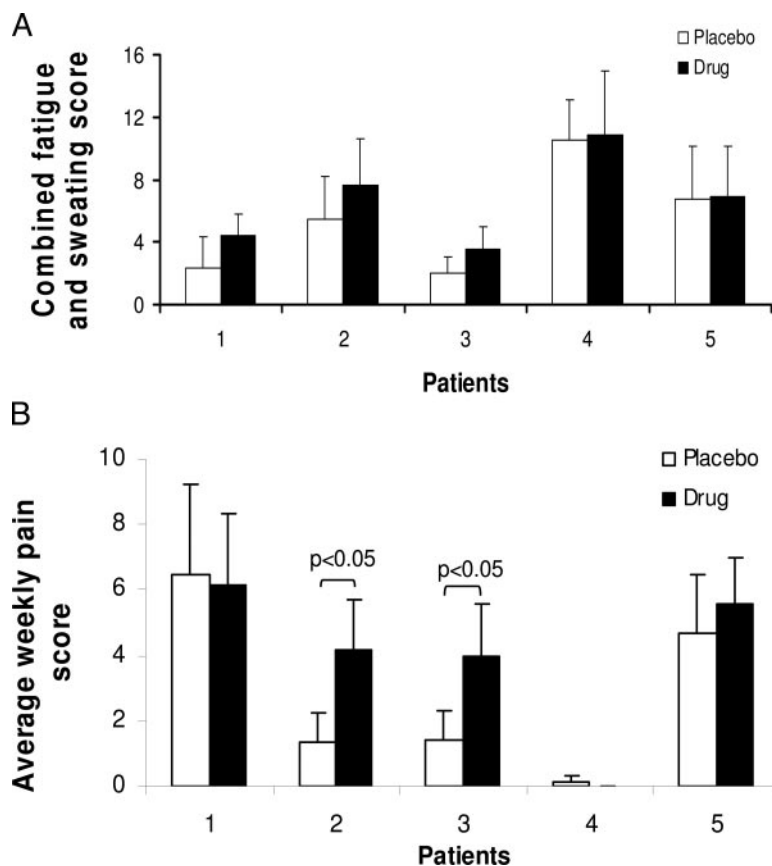


FIG. 3. Sweating, fatigue, and pain scores. Patients kept weekly logs and recorded sweating and fatigue scores (A) and pain scores (B). The mean score  $\pm$  1 SD for each patient on drug (filled bars) and placebo (open bars) are shown. A standardized, validated tool for the assessment of sweating and fatigue was used (see Refs. 15 and 16), and the Brief Pain Inventory was used to assess pain. As a group, there were no differences in sweating, fatigue, or pain, but two patients had significantly more pain on drug than placebo.

Services (Montreal, Canada). Patients kept a weekly diary to record subjective impressions of fatigue and sweating using a visual analog scale ranging from 0 (none) to 10 (worst) (15, 16). Physical examination was performed at baseline and wk 12, 18, 30, and 36. Patients were followed up for at least 12 months after the end of the drug and placebo period.

Secondary skeletal effects of pegvisomant on FD were assessed by measuring markers of bone metabolism and bone pain. Bone pain was measured using a validated, subjective self-assessment tool developed by the American Pain Society, the Modified Brief Pain Inventory (17). Bone metabolism markers (serum alkaline phosphatase, bone-specific alkaline phosphatase, osteocalcin, urine N-telopeptides of collagen, pyridinoline, and deoxypyridinoline cross-links) were measured by standard commercially available assays (Mayo Medical Laboratories).

Pituitary volume was assessed by T1-weighted noncontrast and post-contrast MRI of the brain performed at baseline and 12 months after enrollment. From sagittal and coronal sequences, anterior-posterior, superior-inferior, and medial-lateral measurements were recorded at the maximum dimension to estimate pituitary gland volume.

#### Statistical analysis

Pegvisomant and placebo primary efficacy data were accessed as percentage change from baseline and compared using Fisher's exact test or the  $\chi^2$  test for the comparison of proportions. Continuous measures were compared using the two sample *t* test. Measurements of head

circumference were compared with age and gender-matched controls (18), Z-scores were calculated using assay-specific age and gender-matched reference values (8), and Pearson's linear regression was used to evaluate correlations and degree of significance. Statistical analyses were two sided, and  $P < 0.05$  was regarded statistically significant. All analyses were performed with JMP Windows NT 5.1 statistical package (SAS Institute, Cary, NC).

#### Role of funding source

Pfizer Inc. (Pharmacia), manufacturer of pegvisomant, limited its role to supply of drug, placebo, and funds for patient travel and certain assays. Study design, coordination, patient care and testing, data analysis, and manuscript preparation were the sole responsibilities of the investigators.

#### Results

All patients had signs and symptoms of GH excess including macrocephaly, the degree of which correlated with baseline IGF-I levels ( $R = 0.91$ ,  $P < 0.05$ , Fig. 1). The mean baseline IGF-I for the group was 491 ng/ml.

A daily dose of 20 mg pegvisomant for 12 wk successfully reduced serum IGF-I in all patients at 6 wk [combined mean

TABLE 3. Serum GH and pegvisomant levels, and anti-pegvisomant antibodies

	Placebo		Pegvisomant	
	Week 6	Week 12	Week 6	Week 12
Mean change in GH compared with baseline (%)	−8.6	0.1	−31.9	−4.9
<i>P</i> value (differences between placebo and pegvisomant)			<0.5	<0.7
Mean pegvisomant level (ng/ml)	0	0	23,774	24,211
Anti-pegvisomant antibodies	Negative	Negative	Negative	Negative



**TABLE 4.** Markers of bone metabolism

	Placebo/drug (% change)					Mean % change <sup>a</sup>
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	
Alkaline phosphatase (U/liter) (37–116)	474/366 (–22)	483/539 (11)	1224/970 (–20)	871/833 (–4)	715/515 (–30)	–13
Osteocalcin (μg/liter) (2–15)	107/118 (10)	22/36 (63)	117/109 (–6)	37/35 (–5)	72/40 (–44)	4
N-telopeptides (pmol/μmol Cr.) (0–64)	1049/865 (–17)	1402/1186 (–15)	636/609 (–4)	668/423 (–37)	1900/1053 (–44)	–23
Pyridinoline crosslinks (nmol/mmol Cr.) (18–40)	1008/890 (–12)	198/203 (3)	636/609 (–4)	348/379 (9)	n/a	–1
Deoxypyridinoline crosslinks (μmol/mol Cr.) (5–14)	228/200 (–12)	35/36 (–3)	223/208 (–7)	89/85 (–4)	n/a	7

Normal range is in parentheses in first column. n/a, Not available.

<sup>a</sup> No mean changes from baseline were statistically significant.

difference –263.4 ng/ml (–53%;  $P < 0.005$ ) and 12 wk [combined mean difference of –329.8 ng/ml (–63%;  $P < 0.001$ , Table 2)]. The differences in serum IGF-I between baseline or placebo and drug treatment for each patient, shown as percent changes from baseline, are depicted in Fig. 2. The decrease in IGFBP-3 at 6 wk was significant (combined mean difference 0.8 mg/liter (24%;  $P < 0.01$ ), and 12 wk [combined mean difference –2.0 mg/liter (37%;  $P < 0.001$ , Table 2)], suggesting that serum IGF-I may be a better measure of pegvisomant efficacy. There was no significant difference in the degree of the acromegalic symptoms of fatigue and sweating between the drug and placebo phases (Fig. 3), nor was there a correlation between the severity of these symptoms and the degree of IGF-I elevation (data not shown). Average weekly bone pain score was significantly higher in two patients during pegvisomant treatment, but as a group there was no overall effect on pain (Fig. 3).

There was no change in random serum GH at 6 or 12 wk, antibodies to pegvisomant were undetectable throughout the study, and serum pegvisomant levels confirmed compliance with study drug use (Table 3).

The levels of the markers of bone metabolism were quite high, but there was no significant effect of treatment on either markers of bone formation (alkaline phosphatase and osteocalcin) or resorption (N-telopeptide, pyridinoline, and deoxypyridinoline cross-links; Table 4).

One patient had an increase in pituitary volume over a 12-month period, but as a group, there was no change in pituitary volume (Fig. 4). All the patients completed the study with no adverse events.

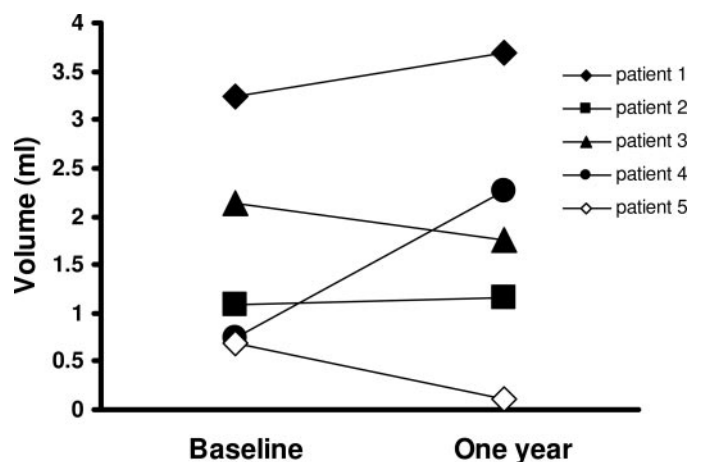
The efficacy of pegvisomant on lowering serum IGF-I was compared with the efficacy of the regimen patients were on before the study. Before the study, all patients were treated with long-acting sandostatin (LAR) ± cabergoline. The mean percent decreases in IGF-I by the pretrial regimen and the pegvisomant were 52 and 63%, respectively (Table 5). One patient who had not been controlled by LAR + cabergoline was controlled by pegvisomant alone.

### Discussion

The medical treatment of a group of patients with GH excess in the context of MAS offers the unique opportunity to study the effects of a drug in a group of acromegalic patients whose disease is of a single molecular etiology, *gsp*.

Successful medical treatment in this group is especially important because these patients are usually not good candidates for surgery due to massive thickening of the skull base with FD, and they are not good candidates for radiation because FD can undergo sarcomatous transformation with radiation treatment. The urgency for successful medical treatment is intensified by the fact that GH excess in FD is an independent risk factor for the development of disfiguring macrocephaly as well as vision and hearing loss, presumably due to GH-stimulated expansion of FD lesions.

We show here that pegvisomant, a GH receptor antagonist, is an effective treatment for GH excess in patients with MAS. It significantly lowered both serum IGF-I and IGFBP-3 in all patients and normalized these values in all but one patient. Whereas this was not a head-to-head trial comparing the efficacy of pegvisomant with other therapies, the efficacy of pegvisomant was retrospectively compared with that of LAR ± cabergoline. As a group there was no difference in the degree of control, but one patient (patient 4) whose IGF-I had not been normalized by a combination of LAR + cabergoline was controlled on pegvisomant alone (Table 5). The single patient whose IGF-I was not normalized by pegvisomant (patient 1) went on to be treated with a combination of both LAR and pegvisomant, and even with this combination, the IGF-I did not normalize. This is different from what was seen



**FIG. 4.** Pituitary volume. The pituitary volume was assessed by MRI at baseline and 12 months later. As a group there was no change in pituitary volume.

**TABLE 5.** Comparison of response to pretrial medication (Rx) and pegvisomant

	Patient no.					Mean % change in IGF-I
	1	2	3	4	5	
Pretrial medical regimen	LAR <sup>a</sup> + CAB <sup>b</sup>	LAR	LAR	LAR + CAB	LAR + CAB	
% decrease IGF-I on pretrial Rx	31	62	62	58	47	–52
% decrease IGF-I on pegvisomant	48	67	58	65	75	–63 <sup>c</sup>
Normalized IGF-I on pretrial Rx	No	Yes	Yes	No	Yes	
Normalized IGF-I on pegvisomant	No	Yes	Yes	Yes	Yes	

<sup>a</sup> LAR, Long-acting somatostatin agonist sandostatin LAR.

<sup>b</sup> CAB, Dopamine agonist cabergoline.

<sup>c</sup> *P* = 0.13 for difference between pretrial medication (Rx) and pegvisomant.

in an earlier study that reported additive effects of pegvisomant in combination with long-acting somatostatin analogs (19). It should be noted that this patient's weight was 127 kg, and his baseline GH and IGF-I were very high, 75.6 and 734 ng/ml, respectively. Given his large body mass and very high baseline GH and IGF-I values, it is possible that the fixed dose (by protocol) of pegvisomant may not have been sufficient to call this a pegvisomant failure. Interestingly, in this group of patients, there was not a significant increase in the serum GH while on pegvisomant (Table 3), as had been reported in other studies (20, 21). The reason for this difference is not known but could reflect that feedback inhibition is lost at baseline in *gsp*-mediated acromegaly and that when IGF-I is lowered by pegvisomant, there is no further loss of feedback inhibition and thus no increase in serum GH. Whereas pegvisomant seems to be marginally better than the pretrial medical regimen, there was no significant difference in response to therapy in patients with *gsp*-mediated GH excess.

Although pegvisomant lowered serum IGF-I and IGFBP-3, it was disappointing that the drug had no effect on the GH excess-related symptoms of fatigue and sweating. It is possible that this lack of effect was due to either the relatively short duration of treatment or the fact that the dose of pegvisomant was not titrated to relief of symptoms. It was reassuring that attenuation of the inhibitory feedback effect of high IGF-I caused no change in pituitary volume as a group, at least during the period under study. It is possible that progression in tumor size that was observed in one patient may be the result of disease progression. This point may be a reflection of the relatively short study length; therefore, as in other medical treatments of GH excess, tumor size should be monitored in patients on chronic pegvisomant treatment.

One of the expectations of this study was that the blockade of GH receptors or the secondary lowering of serum IGF-I would improve FD symptoms as assessed by a decrease in bone pain and/or a decrease in markers of bone metabolism. Whereas there was a trend toward lower levels of markers of bone metabolism, this was not statistically significant, perhaps attributable to the small number of patients studied (Table 4). This is somewhat surprising, given the fact that previous studies have shown that treatment of acromegalic patients, in whom markers of bone turnover were high at baseline, with pegvisomant resulted in reductions of markers of bone turnover (22–24). In addition, there was no improvement in bone pain, and in fact two patients experienced a significant increase in bone pain. It is not clear whether this was related to drug effect or disease progression.

Given the potential for tumor shrinkage by LAR and the established long-term safety of long-acting somatostatin analogs, our recommendation for the initial treatment of GH excess in MAS is a trial of LAR. If this response is inadequate, high-dose dopamine agonist or pegvisomant may be added. If medical therapy is inadequate, and access to the pituitary is not prohibited by bone overgrowth, surgery may be an option. However, even in cases wherein it appears that a single, discreet adenoma is the cause of excess GH, the gland is often diffusely involved with areas of somatotroph hyperplasia, and the only option for surgical cure is total hypophysectomy. The remaining option is radiation, which should also be approached with caution because FD, which always encases the pituitary in MAS, is prone to sarcomatous transformation after treatment doses of radiation (13). This risk may be minimized with technologies using focused beam irradiation.

In summary, pegvisomant effectively controlled GH excess in patients with MAS and was at least as effective as LAR in normalizing serum IGF-I.

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